The science of clinical neurology

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Introduction

I am conscious of the singular honour that the Section of Neurology and the Society have conferred upon me by inviting me to give this twenty-fourth Hughlings Jackson Lecture, 150 years after Jackson was born in Green Hammerton in Yorkshire. A glance at the names of my predecessors fills me with foreboding and with a deep sense of humility and inadequacy, but I am nonetheless most grateful. The terms of the Trust Deed require that the lecture shall be on the science of neurology and it is my aim here to show that even in this era of explosive development in technology and in neuroscience, clinical neurology is still a science which should, and indeed must, be learned by all who practise my specialty, whatever sophisticated instrumentation they may have at their disposal.

Hughlings Jackson (Figure 1) himself can truly be regarded as the founding father of this science. As Peter Schurr pointed out in his Presidential Address to the Section in November 1983[1], Jackson in 1886 became the first elected President of the Neurological Society of London, from which ultimately the RSM Section of Neurology evolved. Jackson's early medical education took place in York, where his father was a general practitioner, but in 1859 he moved to London to qualify formally before returning to work at the York Dispensary. There[2] he was much influenced by Laycock, subsequently Professor of Medicine at Edinburgh, who had in 1841 enunciated the doctrine that the brain is subject to laws of reflex action and did not therefore differ in this respect from other nervous ganglia. When Jackson subsequently returned to London his interest in psychology led him to consider giving up medicine for philosophy, but it was the persuasion of Jonathan Hutchinson which led him to continue in neurology so that he was soon appointed Assistant Physician to the National Hospital, joining the staff of the London Hospital a year later. He was also stimulated by the brilliance in both neurology and physiology of Brown-Séquard.

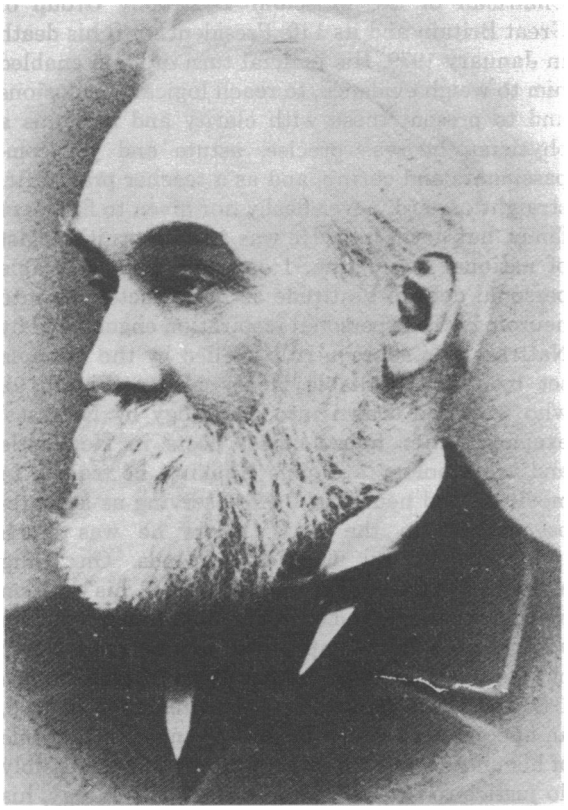

Figure 1. John Hughlings Jackson[2]

It was his grasp of pathophysiological concepts which led Jackson to extend the 1824 observations of Bravais by describing and characterizing the attacks of focal epilepsy now universally known as Jacksonian. His later work on epilepsy was remarkable, not only for his skilful localization of the origin of the attacks, but also for the range of clinical phenomena, including visual loss, arrest of an aura, systematized sensory experiences, abnormalities of taste and smell, depersonalization and psychosensory auras, all of which were fully described. He also made outstanding contributions to knowledge of speech and language, neuro-ophthalmology, aural vertigo, spasticity, rigidity and hypotonia, and was one of the first to distinguish clearly between the clinical effects of lesions of the cerebrum on the one hand and those of the cerebellum on the other. His sense of humour also surfaced in his writings on the psychology of joking. And, of course, we all remember his law of dissolution, which I paraphrase when teaching medical students by saying that the faculties most recently acquired in the process of evolution are generally the first to be lost as the result of a cortical lesion. To demonstrate the truth of this assertion, I have often used that Miller Fisher test for a minimal corticospinal tract lesion which involves tapping on the middle joint of the thumb with the tip of the index finger while holding the remaining fingers still. I once had to point out to an Australian colleague who practised the test assiduously without success that the ability to move individual fingers is one which can only be assessed in relation to one's personal state of evolution.

History of neurology in Newcastle upon Tyne

Having convinced you, I hope, that Jackson, even compared with his outstanding peers, was an incomparable clinical scientist, may I next pay tribute to some contributions made to clinical neurology by a few of those who worked in Newcastle upon Tyne,

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Figure 2. The old Newcastle upon Tyne College of Surgeons[3,4]

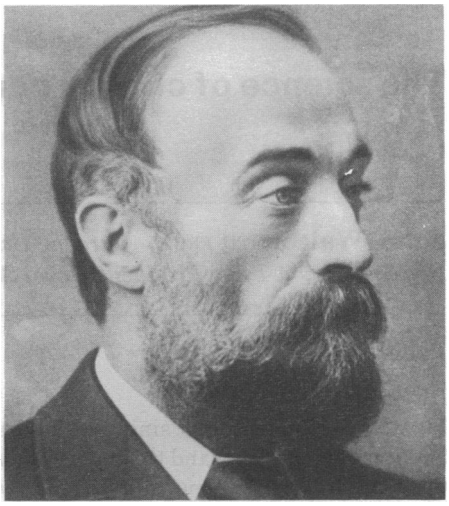

Figure 3. Dr C R Arnison[4]

where in 1984 the medical school celebrated the 150th anniversary of its founding[3,4]. Among those who worked in the old College of Surgeons in Newcastle (Figure 2) was C W Arnison (1837–1899) (Figure 3) who became Professor of Surgery in 1892, shortly after publishing in the *British Medical Journal* of 1891 a case of compound comminuted depressed fracture of the skull with trephining and recovery followed by subsequent epilepsy with retrephining and recovery. He was thus one of the first to treat traumatic epilepsy surgically. He also worked in the old Newcastle Infirmary (Figure 4) on the Forth Banks and was associated with Byrom Bramwell (1847–1931) (Figure 5), the son of a local doctor, who became Lecturer in Clinical Medicine and Pathology in Newcastle and presented several original neurological observations to the local medical society. Later he was appointed Physician to the Royal Infirmary, Edinburgh, in 1874, publishing *Diseases of the Spinal Cord* in 1881 and *Intra-cranial Tumours* in 1888. Bramwell in fact gave the seventh Hughlings Jackson lecture in 1927. Also practising in Newcastle, at about the same time was Sir David Drummond (Figure 6) who wrote extensively on peripheral neuritis and on loss of sensibility in spinal cord disease. He was adjudged to have been the first to recognize an association between syphilitic aneurysm of the aorta and general paresis and his book, *Diseases of the Brain and Spinal Cord* (1883), was very well received. Later he became Vice-Chancellor of Durham University. Throughout his career in the old Newcastle College of Medicine (Figure 7) he was closely associated with the great Robert Howden who, though not principally a neuroanatomist, edited *Gray's Anatomy* for longer than any other editor.

There is even some evidence to suggest that a form of neurology was practised in Newcastle in the late 18th century by Dr Jean Paul Marat, a Frenchman and medical graduate of St Andrew's, who for several years practised in Newcastle what was then known as 'medical electricity'. Later he returned to France and during the Revolution was involved with Charlotte Corday, eventually perishing in the bath. Of much greater distinction, if not neurological, were the anaesthetist and epidemiologist, John Snow, initially apprenticed in Newcastle, and George Murray, who first treated myxoedema effectively with an extract of sheep's thyroid gland in the Royal Victoria Infirmary after it was opened by Queen Victoria in 1900[3,4].

Coming closer to the present day, a most significant Newcastle contributor to neurological knowledge was the late Fred Nattrass (Figure 8), who graduated with first class honours in 1914, served in the RAMC throughout the First World War and was a prisoner in German hands for nine months. After the war he was awarded the Gold Medal for his MD thesis on the diagnosis and treatment of injuries of the peripheral nerves. He gave the Lumleian Lecture on late-onset epilepsy in 1948, and his report on recurring polyneuritis published in the 1920s was acknowledged as being of fundamental importance, antedating current knowledge of relapsing autoimmune polyneuropathy. In the French literature this condition is still known generally as '*le maladie de Nattrass*'. In later years his increasing interest in muscle disease (upon which he gave his Presidential Address to this Section) led to his becoming Chairman of the Muscular Dystrophy Group of Great Britain and its Life President until his death in January 1979. His judicial turn of mind enabled him to weigh evidence, to reach logical conclusions and to present these with clarity and force; as a physician he was precise, astute and yet compassionate and caring, and as a teacher pragmatic, straightforward, never flashy nor given to flights of fancy, but never dull. He was also an ornithologist of national distinction. I owe him a considerable personal debt of gratitude as he attracted me into neurology. That personal inspiration engendered by Nattrass was subsequently fuelled by the example set by the remarkable Henry Miller (Figure 9), who was also drawn into neurology by Nattrass' example. After house officer posts in Newcastle and in pathology at Johns Hopkins, he trained in medicine and neurology before serving as a neuropsychiatrist in the RAF, where he was much influenced by Sir Charles Symonds. On being appointed to the staff of the RVI in 1948, his work on multiple sclerosis and on many other topics won him wide renown; he was appointed to a personal Chair of Neurology in 1964, became Dean of Medicine in 1966 and Vice-Chancellor of the University in 1968, an appointment which he still occupied at the time of his untimely death in 1976. How can one possibly do justice to this remarkable man? His energy, his drive, his remarkable intuitive clinical ability, his

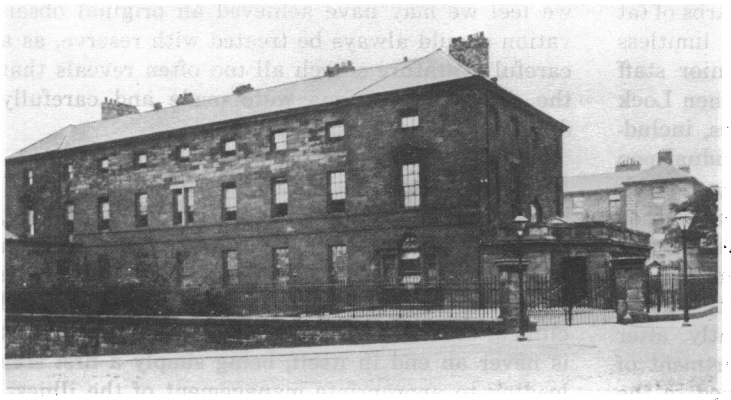

Figure 4. The old Newcatle upon Tyne Infirmary[3]

Figure 5. (right) Sir Byrom Bramwell[3]

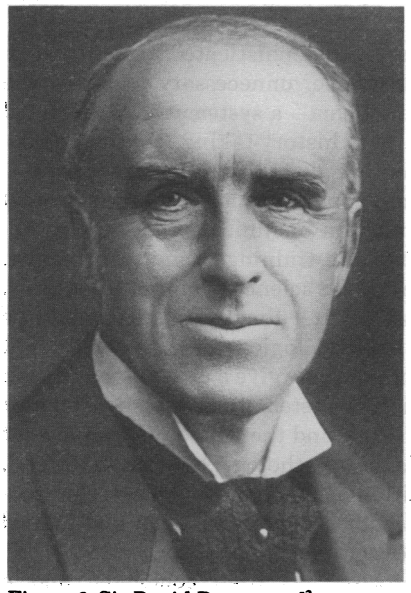

Figure 6. Sir David Drummond[3]

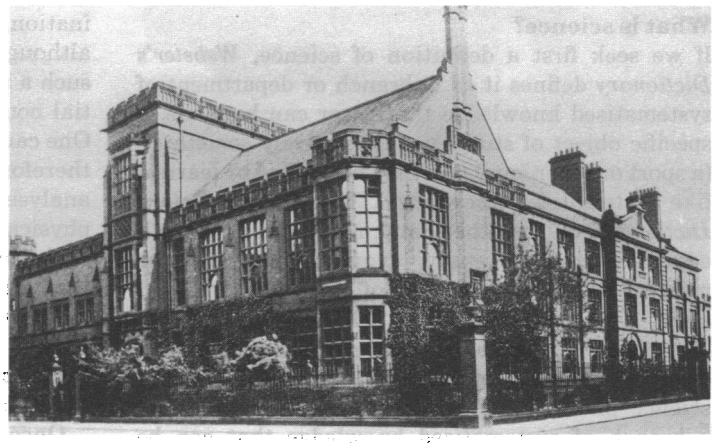

Figure 7. The old Newcastle College of Medicine in Northumberland Road[3]

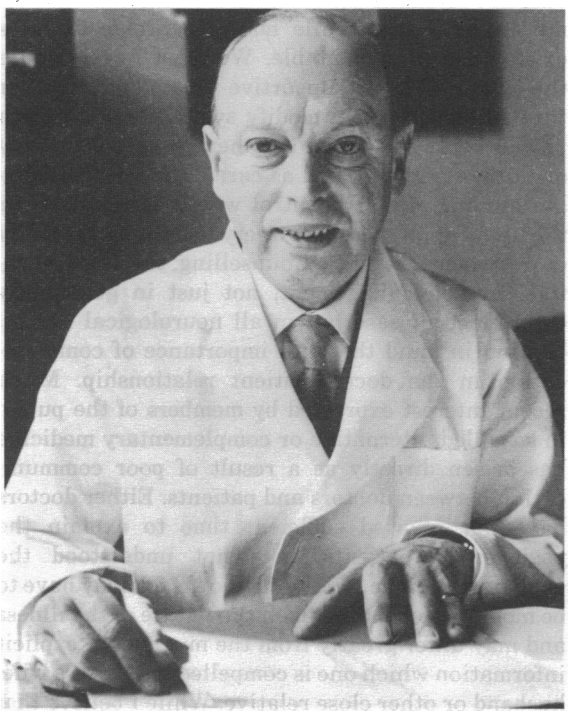

Figure 8. Professor F J Nattrass (photograph by Sir George Smart)

Figure 9. Dr Henry Miller (photograph by Swinton and Wood, Gosforth)

abounding flow of language spiked with barbs of (at times) wounding wit, but above all his limitless generosity to friends, colleagues and junior staff were extraordinary. After his death, Stephen Lock encouraged many of his former colleagues, including myself, to contribute their own individual pen pictures to a volume entitled *Remembering Henry*[5]; this revived many of his delicious quotes, such as 'The best instrument for obtaining the plantar response is the ignition key of a Bentley', or 'Hemiplegic multiple sclerosis is a rarity and is to be diagnosed only by me'. Subsequently, after Henry established the new clinical department of neurology in 1956 at the RVI and I moved to the General Hospital where the Regional Neurological Centre was opened in 1962, I added myself to that list. Henry established a fine tradition of clinical teaching, service and research and I am privileged today to be able to comment upon some of the contributions which Newcastle has made to the science of clinical neurology.

What is science?

If we seek first a definition of science, *Webster's Dictionary* defines it as 'a branch or department of systematised knowledge that is, or can be made, a specific object of study, or alternatively something (a sport or technique) that may be studied or learned like systematised knowledge'. The *Shorter Oxford Dictionary*, on the other hand, regards it as 'knowledge acquired by study; acquaintance with, or mastery of, any department of learning; a trained skill'. If we then turn to the definition of 'clinical', *Webster* defines this as 'involving or depending upon direct observation of the living patient'. Thus the science of clinical neurology can be regarded as a branch of systematized knowledge that can be studied and learned and which can be mastered through direct observation of patients.

Literary definitions, too, are of some interest. Herbert Spencer said that 'science is organised knowledge', while Robert G Ingersoll remarked that 'reason, observation and experience are the holy trinity of science'; I can hardly think of a commentary more apposite to the practice of any branch of clinical medicine, including neurology. But we must not allow science to run ahead of judgment, compassion and human understanding in patient management, and the remark of Oliver Wendell Holmes that 'science is a first-class piece of furniture for a man's upper chamber if he has common sense on the ground floor' is particularly apposite. So, too, was Thomas Jefferson's saying that 'the main object of all science is the freedom and happiness of man'. However, conflicts of view have emerged between the clinical and the physical scientists. Thus I cannot agree with Madame Curie's comment that 'science is the study of things, not of people'. Nor can one wholly accept the wry comment of John Clare that 'science finds out ingenious ways to kill strong men and keep alive the weak and ill'. Nevertheless, this conveys to us a warning, which is now timely, to be cautious in our use of powerful drugs which may have troublesome and even occasionally disastrous side effects. And many centuries ago Geoffrey Chaucer said 'and out of old bokes in good feith cometh all this newe science that men lere'. How right he was in reminding us that the blinding revelations which come to us from time to time when we feel we may have achieved an original observation should always be treated with reserve, as a careful literature search all too often reveals that the same observations were made and carefully documented many years earlier.

Principles of clinical neuroscience

In learning the art and science of clinical neurology, I tell my students that first one must define one's aim and secondly one's method. The aim must surely be to do what is best for one's patient in his personal clinical setting. Diagnosis is the first objective but is never an end in itself, being simply a first step leading to appropriate management of the illness. There are, indeed, some clinical situations where management is perfectly clear, even when exact diagnosis in pathophysiological terms has not been achieved[6].

To an informed and sophisticated audience such as this it is, of course, unnecessary to stress the importance of a schema – a systematic and planned approach to clinical history-taking, physical examination, differential diagnosis and treatment – although I remain convinced that the acquisition of such a firm foundation in clinical skills is an essential component of the training of any neurologist. One can summarize the science of clinical diagnosis, therefore, by saying first that symptoms should be analysed in pathophysiological terms; secondly that physical signs, if any, may give a clue to localization of the focal lesion or system process responsible for the patient's disease, and the tempo of development of the symptoms to its pathology; but that in the end, pattern recognition of syndrome and disease presentation may be crucial, depending upon and fuelled by the fruits of experience[6].

Once this process has been completed and a diagnosis has been reached, or a decision about management made even in the absence of a definitive diagnosis, therapy may consist of specific treatment, whether by drugs or by surgical means. But there are many nervous diseases for which no curative treatment is available. I therefore tell all my students that while many incurable diseases exist, none is untreatable. We must never ignore the importance of supportive treatment, whether through drugs which modify symptoms or through physiotherapy, occupational therapy, speech therapy and other methods such as careful and compassionate nursing, dietary control where appropriate, or the use of appliances or surgery in helping to modify or overcome disability. Counselling, too, is an essential part of management, not just in genetically determined disease but in all neurological illness, bearing in mind the vital importance of communication in the doctor–patient relationship. Much recent interest expressed by members of the public in so-called alternative or complementary medicine has arisen directly as a result of poor communication between doctors and patients. Either doctors have not allowed sufficient time to explain the position or patients have not understood the explanation given. What one should tell may have to be modified depending upon the nature of the illness and may differ greatly from the much more explicit information which one is compelled to give to a wife, husband or other close relative. While I believe that it is never justifiable to tell a direct untruth when a patient, for example, asks 'Am I suffering from

multiple sclerosis?', if no such direct question is posed, it may be reasonable to talk about recurrent 'neuritis' in the early stages of the illness and only to reveal its true nature when it has finally become established on a progressive course. But the spouse may have to be told much earlier. And in a case of motor neurone disease it is my custom to tell the patient that he or she has a disease which we know and recognize well but for which at present we do not have a specific curative treatment. However, I then explain that there are many measures that can be used in the course of the illness to modify its effects or compensate for them. I also say that in most cases the condition progresses for a time and that no one can say how long this will continue. I then suggest that in many cases the condition eventually arrests spontaneously – often temporarily, sometimes permanently. I believe that it is proper not to destroy all hope in the minds of such patients, though I am invariably much more truthful in discussion with appropriate relatives. It is also wise in all such conditions to tell both the patients and relatives of the research being done with the objective of discovering ultimately an effective treatment for the disease. In doing so, it is crucially important not to raise hopes unduly, while leaving some hope alive.

Developments in neurology

Every neurologist, especially those like myself who were medical students when modern neuroradiology was in its infancy, cannot but marvel at the remarkable improvements in diagnostic yield and accuracy achieved by new techniques of brain imaging, including, to quote but a few examples, CT and PET scanning, doppler ultrasonography and now nuclear magnetic resonance. And burgeoning knowledge of neurotransmitters and of their function, as well as the identification of many new types of receptors in the nervous system, have transformed neuropharmacology with outstanding benefit to our patients. New knowledge of pain mechanisms, including not only the gate theory but the recognition of opiate receptors in the brain and the role of endorphins, has helped us to achieve more effective methods of pain control. And despite current inadequacies of provision within the NHS for rehabilitation of the disabled, we have also seen remarkable strides in this field. I shall say more about neuroimmunology in a moment, but in passing we must note the extent to which genetic mechanisms in neurological disease have been illuminated by the discovery of associations with HLA antigens, not only in diseases such as myasthenia gravis and multiple sclerosis, but most recently in the remarkable association between HLA DR2 and narcolepsy reported by David Parkes and his colleagues[7]. Techniques of chromosomal mapping and gene identification, to which I shall also return, have begun to make what is often popularly called 'genetic engineering' a practical possibility.

Are clinical skills redundant?

But to return again to my principal theme, may I stress yet again my view that clinical skills have not been rendered redundant and never will be, as modern investigative methods represent no more than an extension of the clinical examination; they must be planned in the light of pathophysiological analysis and interpreted in the light of clinical findings. To quote but a few examples, I well recall a woman who consulted me with acute attacks of vertigo followed by loss of consciousness which developed when she was hanging out washing on a clothes line. Had not clinical examination revealed a reduced blood pressure in the left arm and bruits in the root of the neck, one might not have considered doing the arch aortogram which showed occlusion of the origin of her left subclavian artery with a subclavian steal syndrome which was subsequently corrected by a vascular surgeon with total relief of symptoms. Similarly, had I not noted in a doctor's wife, whom I was treating for intractable occipital headaches, the development during repeated observation and re-examination of a half-cape of dissociated anaesthesia over the left shoulder with loss of reflexes in the left arm, I would not have planned the supine myelogram (Figure 10) which confirmed that she was suffering from syringomyelia of rapid onset, due to a Chiari type I anomaly. This finding led to surgical decompression at the foramen magnum by John Hankinson, with virtually total relief of symptoms and resolution of the abnormal signs. Similarly, a security officer and former sergeant-major in the Army consulted me with pain in one calf and paraesthesiae in the foot developing during exertion, followed, if he persisted, by foot-drop in the affected leg. Not surprisingly, his general practitioner diagnosed intermittent claudication and a vascular surgeon carried out an aortogram with normal findings. With hindsight, it should have been recognized that while pain is characteristic of ischaemia of lower limb muscles, paraesthesiae and motor weakness are not; the patient's condition was, of course, one of intermittent claudication of the cauda equina, due to lumbar canal stenosis (Figure 11), and again his symptoms were cured by operative decompression. Yet again I recall a patient admitted to hospital with an acute onset of headache, mounting fever, a progressive left hemiparesis and rapidly evolving coma in whom the clinical features strongly suggested an acute right temporal lobe

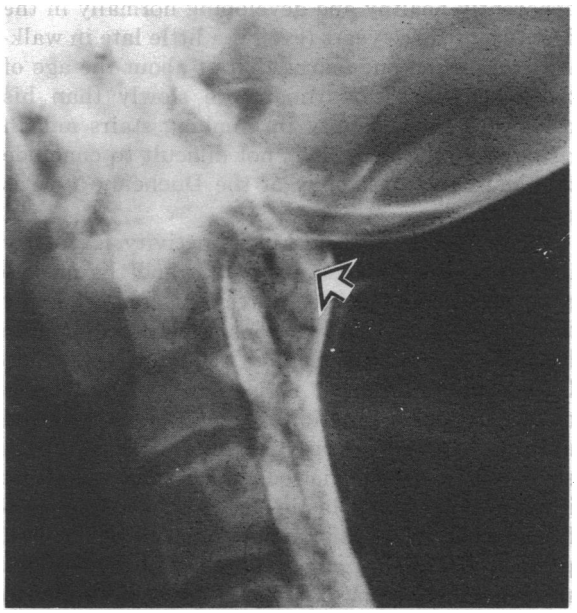

Figure 10. A supine myelogram demonstrating expansion of the upper cervical cord and cerebellar tonsillar ectopia (arrow) causing syringomyelia

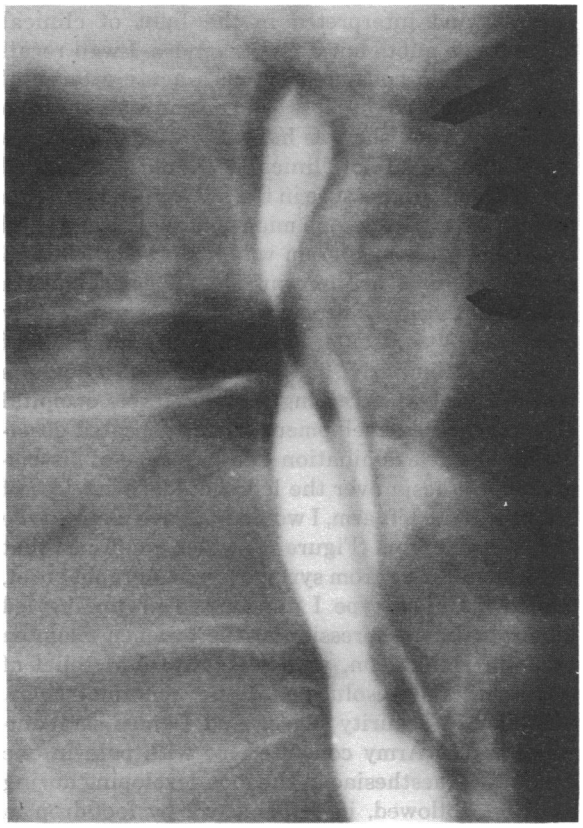

Figure 11. A myelogram demonstrating lumbar canal stenosis causing intermittent claudication of the cauda equina

lesion due to herpes simplex encephalitis. Nevertheless, a vague prodromal history of mild headache and malaise and evidence of skin sepsis counselled caution; the CT scan, especially after enhancement, revealed a large left temporal lobe abscess.

Neuromuscular disease

No doubt those present, aware of my life-long interest in neuromuscular disease, would anticipate that at some stage my interest in this field would intrude, and here too the guiding principles which I have stressed apply equally. When one sees a boy born apparently healthy and developing normally in the first two or three years (even if a little late in walking), and when one learns that at about the age of three he walks and runs more slowly than his peers and has difficulty in climbing stairs and in rising from the floor, it is not difficult to conclude that muscular dystrophy of the Duchenne type is probable.

When serum creatine kinase activity is greatly increased, the EMG is myopathic and the muscle biopsy reveals hyalinized fibres scattered randomly throughout transverse sections, then this diagnosis becomes virtually absolute. About 10 years ago Cullen and Fulthorpe[8] in Newcastle found areas of focal hypercontraction of fibres in unfixed and unstained muscle biopsy samples obtained from early cases when viewed under phase-contrast illumination; thin, plastic-embedded sections confirmed that such contraction bands were indeed present. The hyalinized fibres seen in frozen sections stained with haematoxylin and eosin were due to their having been sectioned through these bands, which either involved the whole transverse section or only a part of it. Concurrently, Mokri and Engel[9] found small defects in the plasma membrane of the muscle cell related to such hypercontracted areas, and it became clear that these allowed an excessive inflow of calcium (probably with associated dysfunction of the sarcoplasmic reticulum) which produced the myofibrillar hypercontraction and also stimulated calcium-activated neutral proteases leading to Z-line loss, myofilament disassembly and phagocytosis (Figure 12).

Unfortunately, the hope that either calcium or protease inhibitors might have a beneficial effect upon the disease process has not been realized[10]. Recently, however, Karpati[11] has suggested that retardation of muscle fibre growth by the deliberate induction of growth hormone deficiency in patients with Duchenne dystrophy might suppress the deleterious effects of the abnormal gene in immature muscle fibres by delaying necrosis and muscle fibre loss. Developments in molecular genetics have, however, had even more exciting consequences, as I shall mention later. In parallel with such work, the longevity of affected boys and their quality of life has been much improved by the provision of appliances and physiotherapeutic management, while carrier detection in the female relatives of affected patients has led to improved genetic counselling with consequent prevention of the birth of new affected boys in families in which cases had occurred, though many new cases continue to arise through mutation[12].

But as I said earlier, we must not forget the crucial importance of diagnostic accuracy in neuromuscular disease when interpreting the results of research and their consequences for management. A girl aged 3 years was sent to me many years ago with a diagnosis of Duchenne dystrophy. There was then still doubt about whether the disease was wholly confined to males, and the occasional expression of true Duchenne dystrophy in females – either with an XO chromosome constitution or with chromosomal translocations – was only just becoming apparent. However, I was sceptical about the diagnosis because, although symptoms were typical, on examination the consistent, selective pattern of muscular involvement which is so characteristic of Duchenne dystrophy was lacking: for example, deltoids were severely affected and biceps brachii was comparatively spared. Hence I was not surprised when her EMG indicated neurogenic atrophy, and a quadriceps muscle biopsy (stained for ATPase at pH 9.4) demonstrated convincing and clear cut

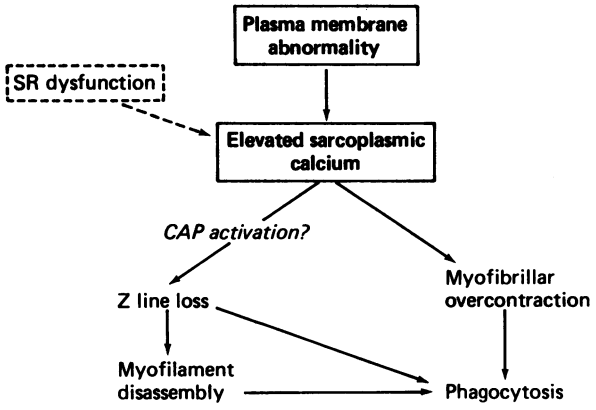

Figure 12. Mechanisms of muscle fibre breakdown in Duchenne muscular dystrophy. (Courtesy Dr M J Cullen)

fibre-type grouping, plainly indicating a denervating process due to spinal muscular atrophy. Similarly, in a young girl of 12, again referred as a case of muscular dystrophy, the fact that her proximal muscular weakness was global and not selective and more severe than the relatively minor wasting would suggest, that her tendon reflexes were well preserved even in weak muscles, that her weakness had developed subacutely and progressed rapidly, and that she had tight, shiny skin on her face with small areas of ulceration extruding calcium over bony prominences, clearly showed that she was suffering from polymyositis. Her condition was treated effectively with steroid drugs. Here were two further circumstances in which careful analysis of symptoms and physical findings was a reliable guide to the diagnoses which were subsequently confirmed by investigation.

Clinical science and laboratory science: a partnership

But if I have given an impression that today's neurologist should be ignorant of, or antipathetic towards, developments in laboratory-based neuroscience, I must at once dispel that illusion, as in my view clinical and scientific neurology are symbiotic and must develop and nurture an ongoing partnership of mutual benefit. The neurologist who allows his clinical skills to atrophy because of increasing dependence upon sophisticated tests, is as out of place in clinical neuroscience as is the blinkered, laboratory-based neuroscientist whose obsession with the acquisition of technical expertise in a restricted field may lead him to ignore messages emerging from clinical science which can illumine the results of his experiments; both are equally culpable. I would like to take two of the examples I have quoted, namely polymyositis and Duchenne muscular dystrophy, as examples of conditions in which a fruitful partnership has benefited both science and patient management.

Neuroimmunology and polymyositis

Immunoregulation

Three major concepts are central to an understanding of immunoregulation[13,14]: these are immunoregulatory T cells, idiotype–antiidiotype networks and immune response genes. One must also recall that each lymphocyte and its progeny stem from individual ancestors with unique membrane receptors which can bind specific antigens. When a lymphocyte is exposed to such an antigen it divides or undergoes clonal expansion. Normally clones reactive against the host's own antigens probably exist but are not operational; when regulatory mechanisms break down and such autoreactive clones proliferate, autoimmune disorders may result.

Immunoregulatory T cells

Different subsets of regulatory T cells are identified through their surface glycoproteins which serve as phenotypic markers for the functional properties of the cell. They consist of suppressor and helper (or inducer) cells (Figure 13). These cells regulate both humoral immunity (B cell production of antibody) and cellular immune responses. Other effector cells including macrophages, neutrophils and mast

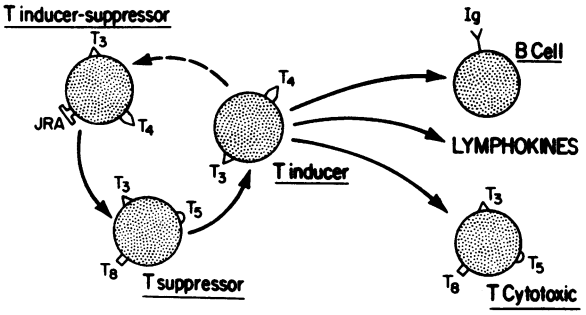

Figure 13. The immunoregulatory T cell network in human beings. Interacting networks of T cells regulate the immune response and can be identified on the basis of surface glycoproteins, which serve as phenotypic markers for the functional properties of the cell. For example, T inducer cells, which bear T4 and T3 markers, induce B cells, which have immunoglobulin (Ig) on their surface, to produce immunoglobulin. B cells without T inducer cells will not produce immunoglobulin when stimulated. If sufficient T suppressor cells (which bear T3, T5 and T8 markers) are added to B cells and T inducer cells, the production of antibody by B cells is shut off. T inducer cells also produce lymphokines, soluble substances that amplify the immune response and induce T cytotoxic cells. Alhough T suppressor and T cytotoxic cells have different functional properties, surface markers have yet to be found that distinguish between these cells. A subgroup of T inducer cells possess the 'JRA' marker (a surface structure reactive with serum from patients with juvenile rheumatoid arthritis). These cells are believed to be inducers of suppressor cells. Based on murine studies, a cell that induces the inducer-suppressor cell (represented by the dotted line) may exist, though it has yet to be described in humans. In summary, all T cells possess the T3 marker, inducer cells possess the T4 marker, and suppressor/cytotoxic cells possess the T5 and T8 markers. (Reproduced from Weiner and Hauser[13] with kind permission)

cells are influenced by these immunoregulatory T cells and their products. Monoclonal antibodies selectively recognize T lymphocyte subpopulations. In man, about 65% of peripheral blood lymphocytes are T cells; the others are B cells, monocytes or cells without T or B cell markers (null cells).

Idiotypes and the network hypothesis

The network theory states that the library of different receptors, whether on T or B lymphocytes, will contain some that can recognize each different and unique receptor site on other receptor molecules. The name given to such a unique receptor site is an idiotype. In an initial random state, the concentration of any one idiotype is too low to stimulate lymphocytes bearing the corresponding antiidiotype; but when the concentration of any given idiotype is increased after stimulation by an antigen, it can stimulate B cells to secrete antiidiotype. Alternatively, it may stimulate T cells which act on cells expressing antiidiotype, either to help or more usually to shut them off[15]. In turn, the antiidiotype molecules stimulate other lymphocytes which express anti-antiidiotypes (Figure 14) and an infinite network of interactions may follow, not only regulating the initial response to antigen but leaving the whole balance altered. It seems that specific suppressor T cells react with the idiotype on helper T cells or B cells, and that the way in which specific T cells stimulate B cells to secrete also involves reacting with the idiotype.

Immune response genes

Most antigens elicit a complex network of functionally distinct T cells that regulate B cells and also each other, and idiotypic–antiidiotypic reactions act within this network. But immune regulation also involves immune response genes, which code for antigens within the major histocompatibility complex (MHC). In animals these gene products probably act in part by determining the way in which macrophages present antigens to T cells, thus influencing whether or not T cells will respond and whether the responding cells will be helper or suppressor. And the gene products can also determine the ultimate T cell repertoire while T cells mature in the thymus, so that susceptibility to autoimmune disease may be strongly influenced by them. The human MHC, of course, contains four major loci, HLA-A, B, C and D. Susceptibility to some diseases is associated with particular haplotypes, the strongest associations being between HLA-B27 and ankylosing spondylitis, and HLA-DR2 and narcolepsy[7]. The D locus seems to be specifically involved in the regulation of suppressor and helper T cell networks.

Abnormalities of immunoregulatory T cells

Abnormalities of immunoregulatory T cells have been found in many human diseases such as lupus erythematosus, juvenile rheumatoid arthritis and haemolytic anaemia. There is conclusive evidence, however, in neurology that there is decreased suppression in multiple sclerosis, confirmed by an abnormal T4/T8 ratio, but not in myasthenia gravis or the Guillain–Barré syndrome; while increased suppression occurs in lepromatous leprosy, cytomegalovirus infection and sarcoid[13]. In polymyositis, while evidence that it is autoimmune seems incontrovertible, the nature of the antigen remains undefined. Certainly it is not myosin, and some have suggested that Z-band protein is important. Several workers, including Simon Currie in Newcastle many years ago[16], demonstrated *in vitro* cytotoxicity upon muscle cells of lymphocytes derived from patients with polymyositis, and although others failed to substantiate these findings, Cambridge and Stern[17] and Isenberg and Cambridge[18] have reported findings conclusively supporting the concept of T-cell-mediated myotoxicity. Rowe and colleagues[19] also identified large numbers of T lymphocytes found in muscle biopsy sections. Arahata and Engel[20,21] have found that muscle fibres in patients with polymyositis are injured by autoinvasive $T8^+$ cells acting in concert with macrophages, along with other findings implying previous sensitization of clones of T cells to muscle fibre-associated surface antigens. There is also evidence that circulating immune complexes play a part and the role of humoral immunity in this disease cannot be ignored. And while viral particles in muscle may be a precipitating factor, it is not yet known how malignant disease acts as such a factor, as it undoubtedly does in patients with dermatomyositis over middle age; thus many unanswered questions remain. Nevertheless, modern immunology has given strong support to the view that steroid drugs and immunosuppressive agents such as azathioprine and possibly cyclosporin[22] in intractable cases are appropriate remedies for use in this disease.

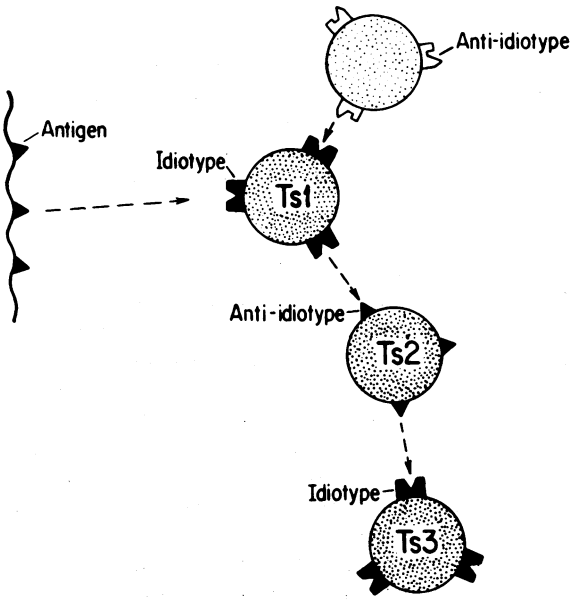

Figure 14. Activation of a suppressor cell network in the mouse. Antigen binds to specific receptors (idiotypes) on the surface of some T cells. These cells, the first-order cells of the suppressor network, are termed Ts1. Ts1 products then react with a second population of cells, Ts2, that possess complementary (antiidiotypic) receptors, or receptors which bind the idiotype. This population in turn reacts with a third subset of cells, Ts3, with anti-antiidiotypic (or idiotypic) receptors. Ts3 appears to represent the active cell that mediates suppression. Note that while the antiidiotype may be antigenically similar to the initial antigen, this is not always the case. (Reproduced from Weiner and Hauser[13] with kind permission)

Duchenne muscular dystrophy and the new genetics

As is well known, Duchenne muscular dystrophy is due to a gene situated on the short arm of the X-chromosome. A carrier female is a woman who has had more than one dystrophic son or who has had a dystrophic brother or other affected male relative on the maternal side of her family and who has an affected son. In such a family, it is important to be able to determine whether sisters of a dystrophic boy or other female relatives are carriers of the mutant gene. To date, carrier detection using serum creatine kinase estimation is imprecise but nevertheless capable, when serum samples can also be obtained from the mother and grandmother of the dystrophic boy and of the girl being tested, of being treated statistically so as to give odds for or against the gene being present in the putative carrier. Within the last three years, DNA recombinant technology and new methods of cytogenetics have produced information of fundamental importance. There are now 9 cases on record in which Duchenne dystrophy, or a disease resembling it, has manifested in a female due to a chromosomal translocation in which part of the short arm of the X-chromosome carrying the gene has become detached and has attached itself to an autosome. Invariably the breakpoint has been in the Xp21 region, and studies of such translocations have helped greatly in the search for the gene (Figure 15). Simultaneously, work has been in progress using flanking markers to map the X-chromosome, and studies of patients with various chromosomal deletions in the Xp21 region have proved invaluable. One marker proximal to the Duchenne locus is that for ornithine carbamoyl

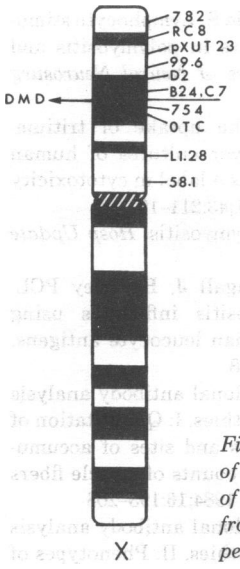

Figure 15. Schematic distribution of RFLP probes along the short arm of the X-chromosome. (Reproduced from Bakker et al.[23] *with kind permission)*

transferase (OTC), deficiency of which gives rise to a specific syndrome in infancy, while another marker (754) which has no known clinical expression lies close to the gene distally. Very recently two further markers, namely C7[23] and p87 (L M Kunkel, personal communication, 1985), have been defined. By using closely linked DNA probes which detect restriction fragment length polymorphisms (RFLPs) distributed over the short arm of the X, Bakker *et al.*[23] detected a double cross-over in a Duchenne dystrophy carrier, and an affected male fetus was diagnosed by chorionic biopsy at 12 weeks of gestation with a probable accuracy of more than 99%. A new mutation was identified in another family with the same degree of reliability, and three females in that family were found not to be carriers. Hence the 11 RFLP markers presently available on the short arm of the X are useful in the diagnosis of DMD as they bridge the Duchenne locus at genetic distances varying between 3 and 20 centimorgans. Even since the report of Bakker *et al.* was published, Kunkel (personal communication, 1985) feels that his new marker p87 lies even closer to the gene than C7. It now also appears that the Duchenne and Becker genes lie at the same locus, differing perhaps only in minor characteristics, and that molecular analysis will allow the gene for both to be identified and characterized, and hopefully sequenced, in the very near future. Current predictions suggest that the gene may not be of very great length.

The practical implications are enormous. First, use of a precise gene-specific marker will allow absolute identification of the carrier female. Secondly, through chorionic biopsy at 10 weeks of pregnancy in a carrier it will be possible not only to sex the fetus but also, using the marker, to identify whether it is a carrier or normal female or an affected or unaffected male. Thus selective abortion of only affected males will become practical. Existing markers make this possible already in some informative families but by no means in all.

Of even greater importance for the future, underlining the reasons why research on the human conceptus up to the fourteenth day must be allowed as Warnock suggested, is the possibility that ova harvested by laparoscopy from a carrier female could be fertilized *in vitro* by her husband's sperm. At the eight-cell stage in the conceptus, it would then theoretically be possible to remove a single cell without harm to the conceptus, to use the gene-specific marker and to identify whether or not the conceptus carries the gene. Implantation of only unaffected male and non-carrier female conceptuses should then be possible. Discovery of the gene will also, of course, lead to examination of its effects, hopefully achieving ultimately methods of modifying or reversing these, but this will be a much longer story.

Epilogue

I hope I have been able to demonstrate in this lecture that clinical neurology is indeed a science which, like any other, has aims and objectives and is governed by sound and definable principles. But clinical and laboratory science are, and must continue to be, partners in our avowed aim of serving to the best of our ability our patients, future patients, knowledge itself and society. And in pursuit of this goal, may I comment upon some of the fashionable but false antitheses which were so effectively demolished by Sir Douglas Black[24] in his Rock Carling Lecture for 1984. Of his many verbal, philosophical and scientific gems I have time to select very few. When Faraday was asked by one sceptical of the value of science, 'What use is electromagnetism?', his response was brief but compelling: 'What use is a baby?', he said. All of us in clinical medicine know that there is no antithesis between the scientific and so-called holistic methods or between the scientific and the compassionate and caring, as all doctors, whatever their training and specialty, surely strive to practise whole-patient medicine. Equally, as several examples I have quoted today indicate, the good doctor is as concerned with disease prevention as with cure. Nevertheless, Black also did us a service in stressing that those who feel that management and business skills may be used to buy results in the ever-changing and ever-challenging field of medical research, must recognize that 'lavish finance can be impotent in the face of unripe time'. This view was expressed alternatively by Parkinson in his 'laws of medical research' which showed that research which does not define precisely a question to be asked, methods of answering it and a route to be followed, may be as fruitless in neurology as is that which goes astray because of deficiencies in clinical knowledge, skills or experience.

Acknowledgments: Figure 1, the portrait of Hughlings Jackson, is reproduced from his collected works[2], Figures 2–7 from Turner and Arnison[3,4], Figure 12 was kindly supplied by Dr M J Cullen, Figures 13 and 14 are reproduced with permission from Weiner and Hauser[13] and Figure 14 from Bakker *et al.*[23] All of the illustrations were prepared in the Audio Visual Centre, the Medical School, the University of Newcastle upon Tyne.

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